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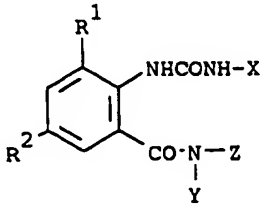
# (54) 2-Ureido-benzamide derivatives

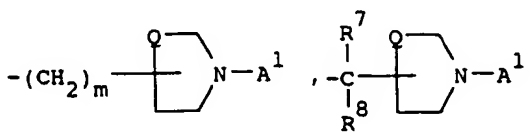
(57) This invention relates to 2-ureido-benzamide compounds of the formula :



(1)

in which $R^1$ is H, halogen atom, $(C_1\text{-}C_4)$alkyl, (C1-C4)alkoxy or (C1-C4)dialkylamino and $R^2$ is H, halogen atom, hydroxy, nitro, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or $-(CH_2)_jNR^3R^3$, wherein j is an integer of from 0 to 2, $R^3$ and $R^4$ are each independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkylsulfonyl or $(C_1\text{-}C_4)$alkylcarbamoyl, or $R^3$ and $R^4$ taken together with the N-atom to which they are linked can form a pyrrolidine, piperidine, morpholine, imidazole or pyrazole ring ;

X is a $(C_3\text{-}C_{15})$alkyl or $-(CH_2)_kNR^5R^6$ group, wherein k is an integer of from 1 to 4 and $R_5$ and $R_6$ are each independently H, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_4)$alkoxycarbonyl ; and,
Y is H or $(C_1\text{-}C_4)$alkyl and Z is



or $-(CH_2)_m—A^2$

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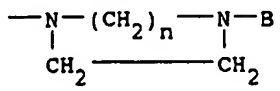
wherein m is an integer of from 0 to 4, Q is $-CH_2-$ or $-CH_2CH_2-$, $A^1$ is phenyl, benzyl, diphenylmethyl, pyridyl, imidazolyl, imidazolylthio, dibenzoxepinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, ($C_1$-$C_7$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkoxymethyl, phenyl or halogenophenyl, $A^2$ is phenyl, benzyl, diphenylmethyl, imidazolylthio, dibenzoxepinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, ($C_1$-$C_7$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkoxymethyl, phenyl or halogenophenyl, $R^7$ is H or ($C_1$-$C_4$)alkyl and $R^8$ is ($C_1$-$C_4$)alkyl, or $R^7$ and $R^8$ taken together with the C-atom to which they are linked can form a cyclopentyl, cyclohexyl or cycloheptyl ring ; or,

Y and Z taken together with the N-atom to which they are linked can form a ring



wherein n is an integer of from 1 to 3 and B is phenyl, diphenylmethyl or dibenzocycloheptenyl optionally carrying halogen atom or ($C_1$-$C_4$)alkoxy ; and pharmaceutically acceptable acid addition salts thereof.

Those compounds are useful as acyl-CoA:cholesterol acyltransferase inhibitors.

## Description

BACKGROUND OF THE INVENTION

1. Field of the invention

The present invention relates to a novel 2-ureido-benzamide derivative having potent acyl coenzyme A:cholesterol acyltransferase(ACAT; EC2.3.1.26) inhibiting activity, to pharmaceutical composition containing these compounds and to use thereof for the treatment and prevention of atherosclerosis.

Ischemic circulatory diseases such as myocardial infarction and cerebral infarction resulting from atherosclerosis have been a major cause of human death. The studies on atherosclerosis have been carried out in the various fields for long years.

Recently, it has been found that esterification of intracellar cholesterol is effectively catalyzed by the enzyme: ACAT which is found later in various tissues such as liver, intestine, adrenal and macrophages. It is said that ACAT may be present in all tissues [The Enzymes, 16, 523-539 (1983)].

In intestine, ACAT plays a key role in the gastrointestinal absorption of cholesterol. In intestinal mucosal cells, dietary and biliary cholesterol derived from the diet and biosynthesis must be esterified by the action of ACAT before it can be incorporated into the chyromicron particules which are then released into the blood stream [Eur. J. Clin. Invest., 9, 55 (1971)]. Thus inhibition of ACAT in intestinal mucosa appears to block intestinal absorption of cholesterol, resulting in the decrease of blood cholesterol level. However, such an intestinal ACAT inhibitor may involve unfavorable increase of the endogeneous cholesterol synthesis and possible ineffectiveness of such inhibitor on patients having no hyperfunction in cholesterol absorption.

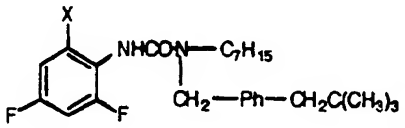
Although the role of ACAT in liver, especially in human, is less clearly known, the ACAT may participate in the synthesis and secretion of VLDL and the control of biliary excretion of cholesterol [J. Lipid Res., 26, 647 (1985)] and inhibition of the liver ACAT may result in lowering of the blood lipid level.

Cholesterol esters are a major component of atherosclerotic lesions and also a major storage form of cholesterol in arterial wall cells. Accumulation of cholesterol esters is linked to the form cell formation which is catalyzed by ACAT in macrophages. Thus, inhibition of the macrpohage ACAT may prevent directly the progression of atherosclerotic lesion formation by decreasing the form cell formation without unfavorable effects as in the case of ACAT inhibition in intestine.

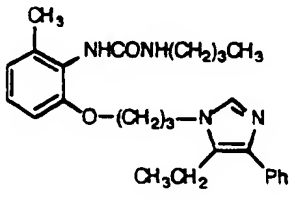
2. Description of the prior art

Certain phenylurea derivatives having ACATinhibiting activity are disclosed as shown below.

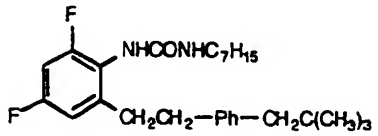
(a) U.S. Patent No.4,623,662 (1986) discloses substituted urea and thiourea compounds such as



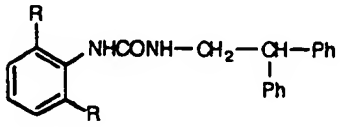

(b) EP Publication No.477,778(1992) discloses benzene, pyridine and pyrimidine derivatives such as



(c) EP Publication No.370,740(1990) discloses diary compounds as inhibitors of ACAT such as



(d) U.S. Patent No.5,116,848(1992) discloses N-phenylalkyl (thio) urea derivatives such as



(e) A variety of urea compounds can be found in the other literatures, for example, in EP Publication Nos.335,375(1989), 405,233(1991) and 447,116(1991) and in U.S. Patent Nos.4,923,896(1990), 5,015,644(1991) and 5,106,873(1992).

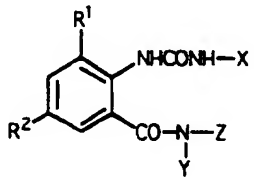
However, there are no known literature references disclosing such 2-ureido-benzamide derivatives as those in this invention and their use as ACAT inhibitors for the treatment of atherosclerosis.

The present inventors synthesized various novel 2-ureido-benzamide compounds having substituents on both of amide and urea(ureido) nitrogen atoms and intensively investigated their activities, and, as the result, found that the compounds have excellent ACAT inhibitory activity and are expected to be useful as a drug for atherosclesosis and related diseases.

## SUMMARY OF THE INVENTION

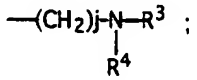
The present invention provides

(i)A novel 2-ureido-benzamide derivative of the formula(1)



(1)

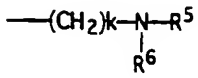
in which $R^1$ is H, halogen atom, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_4)$dialkylamino and $R^2$ is H, halogen atom, hydroxy, nitro, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or



;

wherein j is an integer of from 0 to 2 and $R^3$ and $R^4$ are each independently H,$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkanoyl, $(C_1\text{-}C_4)$alkylsulfonyl or $(C_1\text{-}C_4)$alkylcarbamoyl, or $R^3$ and $R^4$ can be taken together to form pyrrolidine, piperidine, morpholine, imidazole or pyrazole ring;

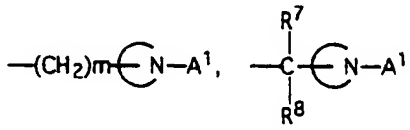
X is a group of $(C_3\text{-}C_{15})$alkyl or



;

wherein k is an integer of from 1 to 4 and $R^5$ and $R^6$ are each independently H, $(C_1\text{-}C_6)$ alkyl or $(C_1\text{-}C_4)$alkoxycarbonyl; and

Y is H or $(C_1\text{-}C_4)$alkyl and Z is

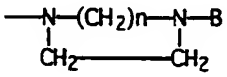


or $-(CH_2)m\text{-}A^2$ ;

wherein m is an integer of from 0 to 4,

is pyrrolidinyl or piperidyl ring and $A^1$ is phenyl, benzyl, diphenylmethyl, pyridyl, imidazolyl, imidazolylthio, dibenzoxepinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, $(C_1\text{-}C_7)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkoxymethyl, phenyl or halogenophenyl, and $A^2$ is phenyl, benzyl, diphenylmethyl, imidazoylthio, dibenzoxepinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, $(C_1\text{-}C_7)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkoxymethyl, phenyl or halogenophenyl, and $R^7$ is H or $(C_1\text{-}C_4)$alkyl and $R^8$ is $(C_1\text{-}C_4)$alkyl or $R^7$ and $R^8$ can be taken together to form cyclopentyl, cyclohexyl or cycloheptyl ring; or

Y and Z can be taken together to form



wherein n is an integer of from 1 to 3 and B is phenyl, diphenylmethyl or dibenzocycloheptenyl optionally carrying halogen atom or $(C_1\text{-}C_4)$alkoxy;

or its pharmaceutically acceptable acid addition salts, having excellent ACAT inhibiting activity;

(ii) An ACAT inhibitor composition which containes any of the compound of formula(1) and its use as the ACAT inhibitor; and

(iii) A method of producing the compound of formula(1).

## DETAILED DESCRIPTION

This invention relates to the compound of formula(1). Referring to the formula(1),the term "halogen" is fluorine(F), chlorine(Cl) or bromine(Br) and the terms "alkyl", "alkoxy" and "alkanoyl" mean straight- and branched-chain alkyl, alkoxy and alkanoyl, respectively. For example, $(C_1\text{-}C_4)$alkyl is methyl, ethyl, n- or iso-propyl, n-, iso-, sec- or tert-butyl; $(C_1\text{-}C_4)$alkylsulfonyl and $(C_1\text{-}C_4)$alkylcarbonyl are sulfonyl and carbonyl substituted by such $(C_1\text{-}C_4)$alkyl, respectively; $(C_1\text{-}C_4)$alkoxy is methoxy, ethoxy, n- or iso-propoxy or n-, iso-, sec- or tert-butoxy; $(C_1\text{-}C_4)$alkoxycarbonyl is carbonyl substituted by such $(C_1\text{-}C_4)$alkoxy; and $(C_1\text{-}C_4)$alkanoyl is acetyl,propionyl or n- or iso-butyryl. Alkyl higher than $C_4$ such as $(C_5\text{-}C_{15})$alkyl may be represented by pentyl($C_5$), hexyl($C_6$), heptyl($C_7$), octyl($C_8$), nonyl($C_9$), decyl($C_{10}$), undecyl($C_{11}$), dodecyl($C_{12}$), tridecyl($C_{13}$), tetradecyl($C_{14}$), pentadecyl($C_{15}$) and their branched-chain form.

Preferred embodiments of this invention represented by the formula(1), in view of such as the ACAT inhibiting properties, exhibit one or more of the following features; (a) $R^1$ is H and $R^2$ is H or di-substituted amino group; (b) X is $(C_3$-

$C_{10}$)alkyl, more preferably, ($C_4$-$C_8$)alkyl; and/or (c) Y is H and Z is (N-aralkyl)aminoalkyl group such as (N-diphenylmethyl)piperidy group with or without intermediary alkylene chain between nitrogen atom of the amide and the piperidyl ring; or Y and Z are combined to form a ring such as (N-diphenylmethyl)piperazinyl ring.

Preferred example of the compounds(1) includes:

- 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-heptylureido)-N-(1-phenoxycarbonylpiperidin-4-yl)benzamde;
- 2-(N'-n-heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide;
- 2-(N'-n-heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-heptylureido)-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylhomopiperazine;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazine;
- 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- N-(2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)benzamide;
- 2-(N'-n-heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- N-(3,3-diphenylpropyl)-2-(N'-n-heptylureido)benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylpiperazine.

The above compounds(1) may be in the form of its pharmaceutical acceptable acid addition salts which are included within the scope of this invention. Preferred example of the salts include salts with inorganic and organic acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, lactic, tartaric, citric, fumaric, malic, maleic, succinic, methanesulfonic, benzenesulfonic and p-toluenesulfonic acids. Preparation of the salts can be carried out in accordance with well known techniques for forming salts.

This invention also relates to a method of or use for reducing the cholesterol content of the arterial walls and treating atherosclerosis and related diseases of mammals which comprises administrating to said mammals an effective amount of a compound as recited above. The compounds(1) have potent ACAT inhibiting activity with weak toxicity as shown in the following test example. ACAT catalyzes the esterification cholesterol with higher fatty acids and it plays an important role in the absorption of cholesterol and in the intracellular accumulation of cholesterol esters. ACAT inhibitor can reduce absorption of dietary cholesterol and intracellular cholesterol ester accumulation in the arterial wall, thereby, lowering the blood cholesterol level with retarding the build-up of atherosclerotic lesions. Accordingly, the compounds(1) of this invention are useful as safe prophylactic and therapeutic agents for hypercholesterolemia, atherosclerosis and diseases resulting from these (e.g. ischemic heart diseases such as myocardial infarction, cerebrovascular diseases such as cerebral infarction and cerebral apoplexy) in mammals (e.g. mouse, rat, rabbit, dog, monkey, human).

This invention further relates to pharmaceutical compositions which comprise an effective anti-atherosclerotic amount of a compound as recited above. For prophylactic or therapeutic use for the above diseases, the compounds of formula(1) are preferably presented with pharmaceutically acceptable appropriate carriers, excipients or diluents as pharmaceutical formulations such as powders, granules, tablets, capsules or injections, which can be prepared by any of the well known techniques of pharmacy and administrated either orally or non-orally.

For the purpose of inhibiting cholesterol absorption or accumulation, the oral route of administration may be preferred. The amount of a compound of formula(1) which is required m achieve the desired biological effect will, of course, depend on the kind of compound(1), the mode of administration, the clinical condition and age of the recipient and the other factors. In general, a daily dose per kilogram of body weight is expected to lie in the range of from 10μg to 10mg, typically from 50μg to 50mg, and such daily dose is preferably administrated as a single dose or in two or three divided doses.

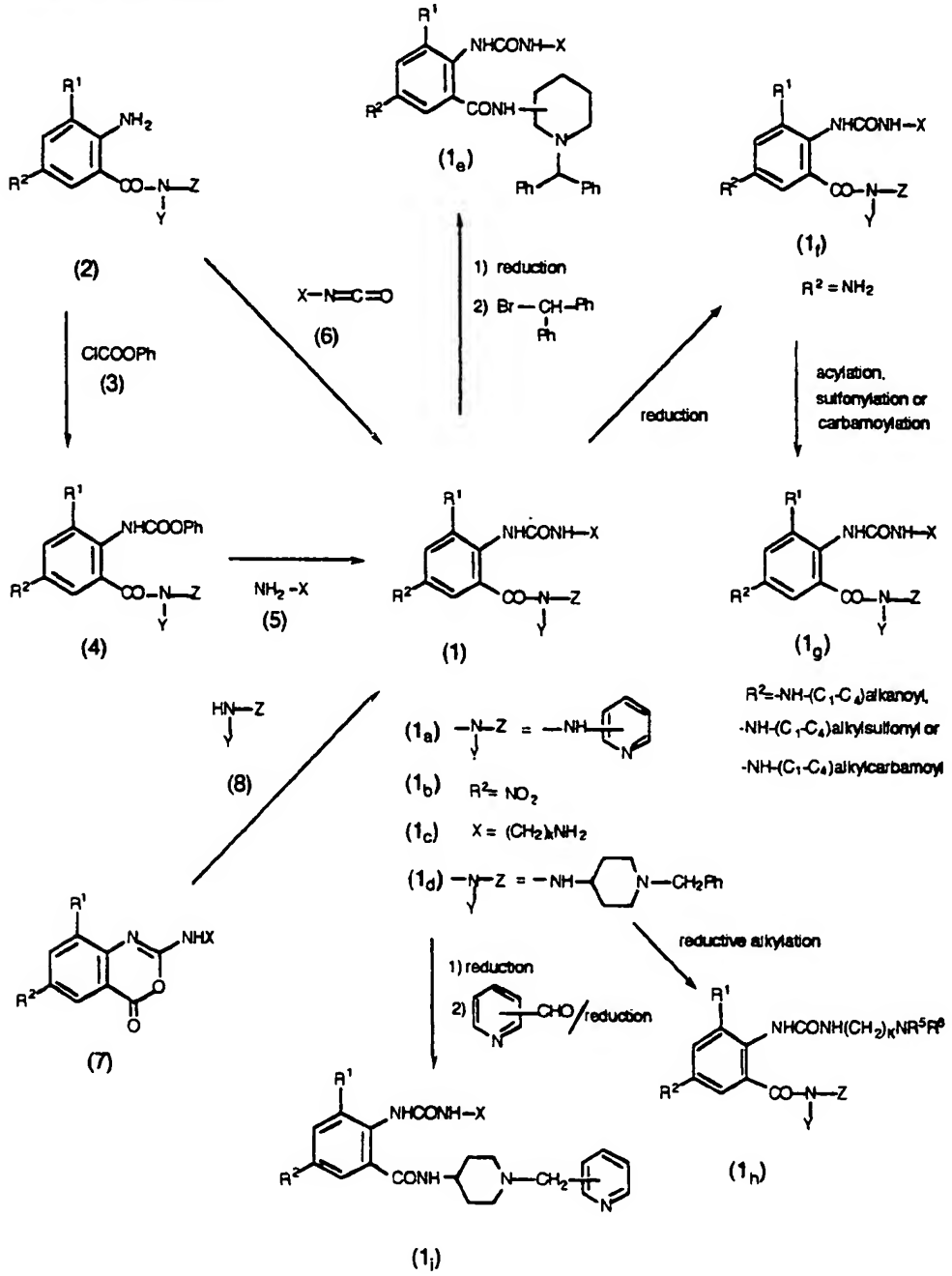
This invention still further relates to process for preparing compounds as recited above.

Preparation Process for the Compound(1)

There are several alternate approaches to the preparation of the compounds in this invention.

A. Synthesis of the 2-ureido-benzamides: 2-Ureido-benzamide derivatives of the formula( 1) can be prepared by, for example, following processes which are outlined in Reaction Scheme I.

**Reaction Scheme I**




(The Symbols in the above formula are as defined hereinabove and phenyl and pyridyl ring may be optionally substituted as defined hereinabove)

A 1) The reaction of the 2-amino-benzamide(2) with formic acid ester halide such as phenyl chloroformate(3) is generally carried out in a solvent in the presence of a base. As example of such base, there may be organic base such as pyridine, triethylamine, picoline, 4 - dimethylaminopyridine and N, N-diethylaniline and inorganic base such as potassium carbonate. Usable as such solvent are any inert to the reaction, for example, benzene, toluene, chloroform and dichloromethane. The reaction is generally conducted at an appropriate temperature of-20°C to the boiling point of a solvent used. The 2-phenoxycarbonylamino-benzamide(4) thus obtained is reacted with the amine (5) to give 2-ureido-benzamide(1). The reaction is generally carried out in an appropriate solvent such as benzene, toluene, chloroform and dichloromethane. The amine(5) may be prepared by known method, for example, by the processes described by C. A Buecheler et. al. in Survey of Organic Synthesis, 394-459(1977) or modifications thereof.

A 2) Alternatively, the 2-ureido-benzamide(1) can be prepared by reacting 2-aminobenzamide(2) with the isocyanate(6). This reaction is conducted in the absence of a solvent or in an inert solvent such as ethyl acetate, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, benzene, toluene and N,N-dimethylformamide. The reaction temperature is generally room temperature to refluxing temperature of a solvent used. In the absence of a solvent, this reaction can be carried out by heating the 2-amino-benzamide(2) with the isocyanate (6) directly at 90-250°C. The isocyanate (6) is obtained by reacting corresponding carboxylic acid with an azide compound such as diphenylphosphoryl azide in the presence of a tertiary amine such as triethylamine, pyridine and picoline in an appropriate solvent such as acetonitrile and chloroform.

A 3) Further, the compound(1) can be prepared by reacting the benzoxazin(7) with the amine(8) in an appropriate solvent such as benzene, toluene, N,N-dimethylformamide, acetonitrile and chloroform. The temperature is generally room temperature to the boiling point of a solvent used. The benzoxazin(7) may be obtained by known method [e. g. J. Heterocyclic Chemistry, 19, 267(1982) and EP Patent No. 147,211 (1985) ] or its modified method. The amine(8) is commercially available or readily prepared by known method described in such as US Patent No. 4,267,318 or modification thereof.

B. Conversion of the 2-ureido-benzamides: Certain compounds of 2-ureido-benzamide derivatives of the formula(1) prepared by the above mentioned processes A1), 2) and 3) are then further converted to the another 2-ureido-benzamide derivatives. For example, the described as the formula ($1_a$), ($1_b$), ($1_c$) and ($1_d$) are successfully converted to the objective 2-ureido-benzamide derivatives of the formulas ($1_e$), ($1_f$), ($1_g$), ($1_h$) and ($1_i$) by following processes which are also outlined in Reaction Scheme I.

B 1) The N-pyridyl-2-ureido-benzamide($1_a$) can be reduced to the corresponding N-piperidyl compound and then reacted with diphenylmethyl halide such as bromodiphenylmethane in the presence of a base such as potassium carbonate in a solvent such as dimethyl sulfoxide to give the N-(N-diphenylmethyl)piperidyl-2-ureido-benzamide ($1_e$). The reduction can be effectively performed by catalytic reduction using an appropriate catalyst such as platinum and platinum oxide under hydrogen atmosphere of an appropriate pressure of 20-100 psi in a solvent such as acetic acid.

B 2) The 5-amino-2-ureido-benzamide($1_f$) may be prepared by reducing 5-nitro-2-ureido-benzamide($1_b$). This reaction can be conducted in the manner of catalytic reduction using appropriate catalyst or can be conducted in the presence of a reducing agent As such catalyst, there may be mentioned, for example, palladium on charcoal, platinum on charcoal and Raney nickel. As examples of said reducing agent is metal(e. g. zinc, iron and tin) in an acid such as hydrochloric acid, acetic acid and aqueous sulfuric acid. The catalytic reduction is generally carried out under hydrogen atmosphere of an appropriate pressure of ambient to 5kg/cm$^2$ in a solvent such as methanol, ethanol, acetic acid and ethyl acetate at an appropriate temperature of room temperature to 100°C. The reaction using the reducing agent is generally carried out in the similar manner to known method described in such as J. Org. Chem., 31, 684(1966).

B 3) Alternatively, 5-amino-2-ureido-benzamide($1_f$) thus obtained may be converted to the 5-N-acylated, 5-N-sulfonylated or 5-N-carbamoylated compound of the formula($1_g$). The compound ($1_f$) can be acylated with an acid anhydride such as acetic anhydride or an acid chloride such as acetyl chloride in the presence of an appropriate base in a solvent such as dichloromethane and chloroform. Useful as said base are organic base, for example, triethylamine, pyridine and N,N-diethylaniline. The reaction temperature is generally 0°C to the boiling point of a solvent used.

Sulfonylating the compound($1_f$) can be performed in the similar manner as the above mentioned acylating, but replacing acid anhydride or acid chloride with alkylsulfonyl chloride such as methanesulfonyl chloride.

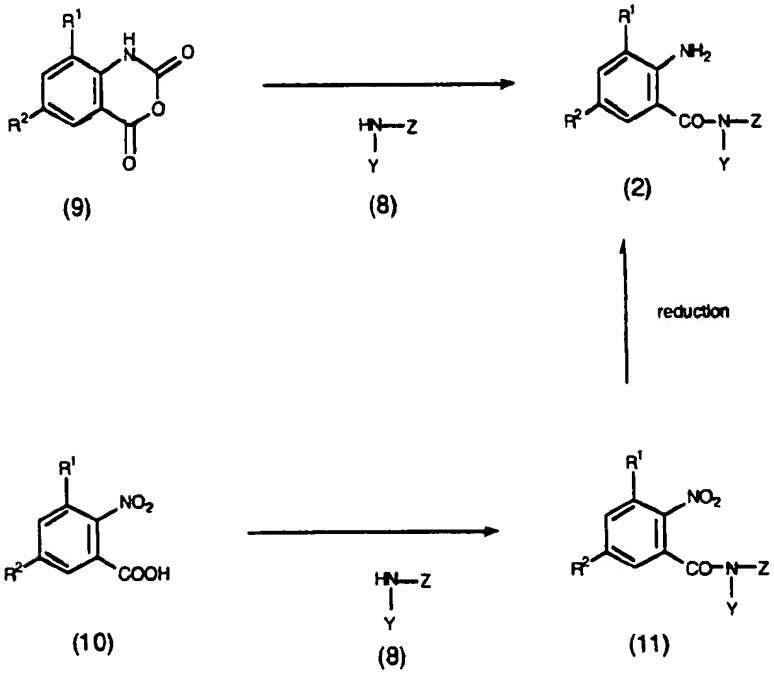
The compound($1_f$) can be converted to the 2,5-diureido-benzamide according to the similar manner as for the preparation process A2) by reacting with the corresponding isocyanate.

B 4) 2-(N'-Alkylaminoalkylureido)-benzamide($1_h$) may be prepared by reductive alkylation of the 2-(N'-aminoalkylureido)benzamide(1c) with the corresponding carbonyl compound. The reaction can be carried out by the use of reducing agent such as sodium cyanoborohydride, sodium borohydride or lithium cyanoborohydride in an appropriate solvent such as methanol, ethanol and ethyl ether at an appropriate temperature of -20°C to the boiling point of a solvent used.

B 5) The benzyl group of the N-benzylpiperidyl-2-ureido-benzamide($1_d$) is removed by reduction and the resulting N-piperidyl-2-ureido-benzamide may be reacted with the corresponding formyl pyridine in the presence of reducing agent such as sodium cyanoborohydride to give the N-pyridylmethylpiperidyl-2-ureido-benzamide($1_i$). The reduction of the compound($1_d$) is generally performed by hydrogen over an appropriate catalyst such as palladium on charcoal.

C. Preparation of the intermediates: The 2-amino-benzamide(2) which is important as a starting compound for the preparation of the 2-ureido-benzamide(1) can be synthesized, for example, by the following processes outlined in Reaction Scheme II.

**Reaction Scheme II**




(9) (8) (2)

(10) (8) (11)

(The Symbols in the above formula are as defined hereinabove)

C 1) 2-Amino-benzamide(2) can be prepared by reacting the isatoic anhydride(9) with the amine(8) in a solvent such as dichloromethane and chloroform at an appropriate temperature of room temperature to the boiling point of a solvent used.

C 2) The condensation reaction of the 2-nitrobenzoic acid (10) with the amine (8) can be carried out in the presence of a condensing agent in an inert solvent such as dichloromethane, chloroform and tetrahydrofurane at an appropriate temperature of 0°C to room temperature. Useful as said condensing agent are 1,3-dicyclohexylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide and 1,1-carbonyl-diimidazole. The 2-nitroben-

zamide (11) thus obtained is reacted with a reducing agent to give the 2-amino-benzamide(2). This reductive reaction can be conducted essentially in the same manner as the preparation process B2) mentioned above.

The desired compounds(1) thus obtained can be purified and recovered by using per se known separation or purification procedures (e. g. concentration, solvent extraction, column chromatography, recrystallization).

Activity

The following pharmacological test results indicate that the 2-ureido-benzamide derivatives(1) according to the inventions are of great utility. 1. Acyl-CoA:cholesterol acyltransferase (ACAT) inhibiting activity.

[Test method]

(1)In-vitro test using Hep G2 microsome.

ACAT enzyme fraction was prepared from microsome of human derived hepatoma Hep G2 cell according to Sandra's method [Journal of Lipid Research 27, 875 (1986)].

Microsome was suspended at a concentration of 200μg protein/ 20μl in 0.1 M phosphate buffer solution(pH7.4) and the suspension was preincubated at 37°C for 5 minutes after addition of 10μl of each test compound dissolved in 0.1M phosphate buffer solution containing bovine serum albmin(BSA). Then, the reaction was initiated by the addition of 5nmoles of labeled [$^{14}$C]-oleoyl-CoA dissolved in 20μl of the said phosphate buffer solution containing BSA and the reaction was stopped by the addition of 20μl of 2N HCl after 10 minutes. [$^{14}$C] cholesterol-oleate formed was separated by thin-layer chromatography and the radioactivity was counted with liquid scintillation counter.

ACAT inhibitory activities of the test compounds were shown as $IC_{50}$ values.

(2)In-vitro test using THP-1 intact cell.

About 2 million cells of human leukemia cell line, THP-1 were seeded in a well with 2ml of medium and differentiated into macrophage-like cells by phorbol ester. Then, the cells were washed with phosphate-buffered saline(PBS) solution and the medium was replaced by fresh medium supplemented with 10% of lipoprotein-deficient serum. After the addition of each test compound dissolved in dimethyl sulfoxide and 100μg protein-containing human low density lipoprotein(LDL), the reaction was initiated by the addition of 10nmoles of labeled [$^{14}$C]oleic acid and 10moles of oleic acid complexed with BSA in PBS solution. After 22 hours, the reaction was stopped by removal the medium and $CHCl_3$-MeOH(2:1) were added to the cell suspension in order to extract lipids.

Intracellular [$^{14}$C] cholesterol-oleate formed was separated by thin-layer chromatography and the radioactivity was counted with lipid scintillation counter.

ACAT inhibitory activities of the test compounds were shown as $IC_{50}$ values.

(3)In-vivo test using mouse peritoneal macrophages.

Male mice were fed a standard powder diet containing the test compounds for 16 days. After 14 and 15 days on this diet, aggregated-LDL (containing 4mg cholesterol) prepared from LDL receptor deficient KHC rabbit and [$^{14}$C]oleic acid together with the said aggregated-LDL (containing 0.5mg cholesterol) were injected into the peritoneal cavity of these animals, respectively. After 16 days on this treatment, peritoneal macrophages were harvested by peritoneal lavage with PBS solution and $CHCl_3$-MeOH(2:1) were added to the cell suspension in order to extract lipids. Formed [$^{14}$C]cholesterol oleate was separated by thin-layer chromatography and the radioactivity was counted.

ACAT inhibitory activities of the test compounds were shown as inhibiting percentage referred to control group.

[Results]

(1) and (2): As can be seen in Table1, the compounds caused a significant inhibitory activity on ACAT.

(3): As can be seen in Table2, the compounds caused a significant inhibitory activity on ACAT.

Table 1

| Test compoud (Example No.) | $IC_{50}$ (μM) | |
|---|---|---|
| | Hep G2 (microsome) | THP1 (intact cell) |
| 1 | 0.6 | 0.007 |
| 2 | 1.0 | 0.1 |
| 3 | 0.9 | 0.1 |
| 4 | 0.9 | 0.09 |
| 5 | 1.6 | 0.07 |
| 6 | 1.6 | 0.05 |
| 12 | 8.0 | 0.7 |
| 19 | 3.6 | 0.1 |
| 28 | 1.2 | 0.1 |
| 29 | 1.6 | 0.2 |
| 30 | 1.2 | 0.2 |
| 31 | 0.8 | 0.2 |
| 45 | 2.8 | 0.8 |

$IC_{50}$ value of ACAT inhibitors on ACAT of HepG2 and THP cells.

Table 2

| Test compound (Example No.) | Inhibition rate(%) (macrophages) |
|---|---|
| 1 | 65 |
| 5 | 64 |
| E5324*a | 38 |
| CI976*b | 50 |

Inhibition rate on ACAT of macrophage

*a:N-[6-methyl-2-{3-(5-ethyl-4-phenyl-1H-imidazol-1-yl)propoxy}]phenyl-N'-butylurea

*b:2,2-dimethyl-N-(2,4,6-trimethoxyphenyl)dodecanamide

2. Test for toxicity.

[Test method]

Acute toxicity: Nine compounds(Example No. 1, 2, 5, 6, 12, 19, 28, 31 and 45) were tested by using male ICR strain mouse weighing 23.0±0.7g. Each test compound was suspended with 0.5% CMC-Na and orally administered in a dose of 1000mg/10ml/kg of body weight, and general signs were observed for seven days. Seven days after administration of each test compounds, no macroscopic changes were observed on any organs at autopsy.

[Results]

No toxicological findings were observed in each test compound treated group.

The following Preparations and Examples are further illustrative of the present invention. It is to be noted, however, that such Examples are by no means imitative of the scope of the invention. All compounds were identified by proton NMR spectrometry, mass spectrometry and/or other analytical or physical technique.

Preparations

Preparation 1 to 11 are described for synthesis of the amine (8) and Preparation 12 to 20 are described for synthesis of the 2-amino-benzamide(2), both of which are intermediates for the preparation of the objective 2-ureido-benzamide(1).

PREPARATION 1

4-Aminomethyl-1-diphenylmethylpiperidine

Step 1): Bromodiphenylmethane (2.5g, 0.01mol) in DMF (10ml) was added dropwise at 0 - 5°C to a mixture of isonipecotamide (1.3g, 0.01 mol) and $K_2CO_3$ (1.4g) in DMF (25ml). The reaction mixture was stirred for 2hours at 0 - 5° C, then poured into water. The mixture was extracted with ethylether, then the extract was washed with brine, dried ($MgSO_4$) and evaporated to give 1-diphenylmethylpiperidine-4-carboxamide (66%): mp 150°C.

Step 2): 1-Diphenylmethylpiperidine-4-carboxamide (1.5g, 5.1mmol) was added dropwise to a suspension of $LiAlH_4$ (0.4g, 10.5mmol) in THF (30ml). The mixture was heated at 70 °C for 3 hours and then cooled. To the mixture, water (0.4ml), 15 % NaOH solution (0.4ml) and water (1.2ml) were added dropwise in order, and insoluble materials were filtered off. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane) to give 4-aminomethyl-1-diphenylmethylpiperidine (57.0%) as colorless crystal: mp 80°C.

PREPARATION 2

4-(2-Aminoethyl)-1-diphenylmethylpiperidine

Step 1): In a similar manner to that of Preparation 1, but replacing isonipecotamide and 1-diphenylmethylpiperidine-4-carboxamide with ethyl isonipecotate and ethyl 1-diphenylmethyl-4-piperidinecarboxylate respectively, 1-diphenylmethyl-4-hydroxymethylpiperidine was prepared.

Step 2): $SOCl_2$ (0.6ml, 8.2mmol) was added dropwise to a solution of 1-diphenylmethyl-4-hydroxymethylpiperidine(1.0g, 3.6mmol) in benzene (7ml) at room temperature. The mixture was refluxed for 18 hours and then concentrated. The residue was dissolved in ethyl acetate, washed with 5 % NaOH solution, dried ($MgSO_4$) and concentrated. The residue was recrystallized (ethyl acetate/ether /hexane) to give 1-diphenylmethyl-4-chloromethylpiperidine (70.1%): mp 73-75 °C.

Step 3): NaCN (2.5g, 51 mmol) was added to a solution of 1-diphenylmethyl-4-chloromethylpiperidine (8.9g, 29.7mmol) in dimethyl sulfoxide (DMSO) (100ml). The mixture was heated at 60 °C for 20 hours and then poured into 3% $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give 4-cyanomethyl-1-diphenylmethylpiperidine (61.4%): mp 103-104°C and 3-(2-cyanoethyl)-1-diphenylmethyl pyrrolidine (20.9%): oil.

Step 4): In a similar manner to that of Preparation 1 Step 2), but replacing 1-diphenylmethylpiperidine-4-carboxamide with 4-cyanomethyl-1-diphenylmethylpiperidine , 4-(2-aminoethyl)-1-diphenylmethylpiperidine was obtained as oil.

PREPARATION 3

4-(3-Aminopropyl)-1-diphenylmethylpiperidine

Step 1): In a similar manner to that of Preparation 1 Step 1), but replacing isonipecotamide with 4-(2-hydroxyethyl)piperidine 1-diphenylmethyl-4-(2-hydroxyethyl)piperidine was prepared.
Step 2): In a similar manner to that of Preparation 2 Step 2) to 4), but replacing 1-diphenylmethyl-4-hydroxymethylpiperidine with 1-diphenylmethyl-4-(2-hydroxyethyl)piperidine, 4-(3-aminopropyl)-1-diphenylmethylpiperidine was prepared.

PREPARATION 4

3-(3-Aminopropyl)-1-diphenylmethylpyrrolidine

In a similar manner to that of Preparation 1 Step 2), but replacing 1-diphenylmethylpiperidine-4-carboxamide with 3-(2-cyanoethyl)-1-diphenylmethylpyrrolidine which was obtained according to Preparation 2 Step 3), 3-(3-aminopropyl)-1-diphenylmethylpyrrolidine was prepared.

PREPARATION 5

1-Diphenylmethyl-homopiperazine

In a similar manner to that of Preparation 1 Step 1), 1-diphenylmethylhomopiperazine was prepared from homopiperazine and bromodiphenylmethane.

PREPARATION 6

4-(10,11-Dihydrodibenzo[a,d]hepten-5-yl)piperazine

In a similar manner to that of Preparation 1 Step 1), 4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine was prepared from piperazine and 5-chlorodibenzosuberane.

PREPARATION 7

11-Aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin

A solution of $AlCl_3$ (1.0g, 7.5mmol) in dry ether(10 ml) was added rapidly to a solution of $LiAlH_4$ (0.5g, 13.2mmol) in dry ether (13ml). After 5 minutes, a suspension of 2-bromo-11-cyano-6,11-dihydrodibenz[b,e]oxepin (2.0g, 6.7mmol) in dry ether (100 ml) was added to the mixture of hydride. The reaction mixture was stirred for 4.5 hours. Water and Rochelle Salt were added to the reaction mixture. The mixture was poured into ether. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel to give 11-aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin(48.9%).

PREPARATION 8

11-(4-Aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin

Step 1): A solution of 2,11-dibromo-6,11-dihydrodibenz[b,e]oxepin (8.0g, 22.7mmol) in benzene (100ml) was added by portions to the solution of 1,4-dioxa-8-azaspiro[4, 5]decane (6.5g, 45.4mmol) in acetonitrile (50ml) in an ice bath. The reaction mixture was stirred at room temperature for 1 hour and then poured into water. The organic layer was washed with water, then dried ($MgSO_4$) and concentrared to give 11-(1,4-dioxa-8-azaspiro[4,5]decane-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (89.6%).
Step 2): A suspension of 11-(1,4-dioxa-8-azaspiro[4,5]decane-8-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin(5.5g, 13.2mmol) in 4N HCl was heated at 60-70°C for 30 minutes. Then ethanol was added to the mixture. The mixture was heated at 60-70°C for 1.5 hours. After ethanol was evaporated, the reaction mixture was made alkaline with 50% NaOH solution, then extracted with ethyl acetate and chloroform. The organic layer was washed with water, dried ($MgSO_4$) and concentrated to give 11-(4-oxopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (100%): mp 196-200 °C.

Step 3): A suspension of $NH_2CH \cdot HCl$ (1.22g, 17.5mmol) in ethanol (15ml) was added to the solution of 11-(4-oxopiperidin-1-yl)-2-bromo-6,11-dihydro-dibenz[b,e]oxepin (6.5g, 17.5 mmol) in ethanol (100ml) under refluxing. The reaction mixture was refluxed for 1 hour, then concentrated. The residue was suspended with saturated $NaHCO_3$ solution and then extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and concentrated to give 11-(4-hydroxyiminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin(100%): mp 223-225 °C.

Step 4): $LiAlH_4$ (0.14g, 3.7mmol) was added to a solution of 11-(4-hydroxyiminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (1.5g, 3.7mmol) in dry THF (50ml) under nitrogen atmosphere. The reaction mixture was heated at 60-70 °C for 3 hours. After cooled at 0°C, the reaction mixture was hydrolyzed with water and diluted with ether, then filtered. The filtrate was concentrated to give 11-(4-aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin(69.1%): mp 142-144°C.

PREPARATION 9

2-[2-(4-Aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole

Step 1): 1-Bromo-2-chloroethane (10.0g, 0.07mmol) was added by portions to a solution of 1,4-dioxa-8-azaspiro[4,5]decane (1.0g, 7.0mmol) and $Et_3N$ (0.7g, 7.0mmol) in acetonitrile (10ml) at 0°C. The mixture was stirred at 0°C for 48 hours, poured into ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated to give 8-(2-chloroetyl)-1,4-dioxa-8-azaspiro-[4,5]decane (0.914g, 63.5%) as solid.

Step 2): NaH(0.213g, 8.8mmol) was added to a suspension of 4,5-diphenyl-2-imidazolethiol (1.12g, 4.4mmol) in THF (30ml). The mixture was refluxed for 1 hour. To the reaction mixture, 8-(2-chloroethyl)-1,4-dioxa-8-azaspiro[4,5]decane (0.914g, 4.4mmol) was added at 0°C under stirring and refluxed 24 hours and then concentrated. The residue was poured into water and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The precipitate was recrystallized (toluene) to give 2-[2-(1,4-dioxa-8-azaspiro[4,5]decane-8-yl)ethyl]thio-4,5-diphenylimidazole (0.970g, 52.3%).

Step 3): A suspension of 2-[2-(1,4-dioxa-8-azaspiro[4,5]decane-8-yl)ethyl]-thio-4,5-diphenylimidazole(0.86 g, 2.0 mmol) in concentrated HCl (20 ml) was heated at 60 °C for 2 hours. The reaction mixture was made basic with 10% NaOH solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 2-[2-(4-oxopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (0.75g, 98.7%) as clear oil.

Step 4): Sodium cyanoborohydride (0.06g, 9.5mmol) was added to solution of 2-[2-(4-oxopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (0.34g, 0.91mmol), powdered 3A molecular sieves (0.268g) and ammonium acetate (0.73g, 9.5mmol) in methanol (10ml). The mixture was stirred at room temperature under nitrogen atmosphere for 65 hours and then filtered and washed with methanol. The filtrate was concentrated. The residue was dissolved in 10% NaOH solution and ethyl acetate. The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (0.8% $NH_4OH$ in chloroform/methanol) to give 2-[2-(4-aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (172mg, 49.9%) as pale yellow oil.

PREPARATION 10

2-(2-Aminoethylthio)-4,5-diphenylimidazole

60 % NaH in oil (0.91g, 22.8mmol) was added to a suspension of 4,5-diphenyl-2-imidazolethiol (2.5g, 9.9mmol) in dry THF (80ml) at room temperature under stirring. After 15 minutes, 2-bromoethylamine hydrobromide (2.0g, 9.9mmol) was added to the mixture. The reaction mixture was refluxed for 1 hour, then poured into water (500ml) and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated. The residue was recrystallized (toluene) to give 2-(2-aminoethylthio)-4,5-diphenylimidazole (51.3%): mp 152-154 °C.

PREPARATION 11

1-(2-Aminoethyl)-4,5-diphenylimidazole

Step 1): A solution of 4,5-diphenylimidazole (2.5g, 11.3mmol) in dry DMF (20ml) was added to a suspension of NaH (0.33g, 13.8mmol) in dry DMF (5ml) at 50°C under nitrogen atmosphere. The reaction mixture was heated at 60 °C for 2 hours. After heating, the mixture was added dropwise to a solution of 1-bromo-2-chloroethane (4.9g, 33.9mmol) in dry DMF (30ml) over 1 hour at 50 °C. The reaction mixture was heated continuously at 40 °C for 5 hours, then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitates were filtered off. The filtrate was concentrate The residue was purified

by column chromatography on silica gel (ethyl acetate and hexane) to give 1-(2-chloroethyl)-4,5-diphenylimidazole (17.7%).

Step 2): A mixture of potassium phthalimide (0.21g, 1.1mmol) and 1-(2-chloroethyl)-4,5-diphenylimidazole (0.32g, 1.1mmol) in dry DMF (10ml) was heated at 60-70°C for 6 hours. The reaction mixture was cooled, diluted with chloroform, poured into water and extracted with chloroform. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (40% ethyl acetate in chloroform) to give 1-(2-phthalimidoethyl)-4,5-diphenylimidazole (73.0%).

Step 3): 80% Hydrazine monohydrate (0.062ml, 1.3mmol) was added to a solution of 1-(2-phthalimidoethyl)-4,5-diphenylimidazole(0.32g, 0.8mmol) in methanol (20ml) under refluxing. The reaction mixture was refluxed for 1 hour, then cooled. The mixture was made acidic slightly with 6N HCl and then filtered to remove phthalhydrazide. The filtrate was concentrated and then the residue was suspended in 2N NaOH. The suspended mixture was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The precipitates were recrystallized (ethyl acetate/ hexane) to give 1-(2-aminoethyl)-4,5 - diphenylimidazole (88.1%): mp 96-98 °C.

PREPARATION 12

2-Amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

Step 1): A mixture of 5-dimethylamino-2-nitrobenzoic acid [J. Med. Chem., 24, 742 (1981)](9.0g, 40mmol), 4-aminomethyl-1-diphenylmethylpiperidine (12.0g,40mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) (8.0g, 40mmol) and 4-dimethylaminopyridine (DMAP) (5g, 40mmol) in dichloromethane (400ml) was stirred at 0°C for 1 hour, then at room temperature for 3 days. The reaction mixture was washed with 1N HCl, then water. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (5% methanol in dichloromethane) to give 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (47%) as yellow solid: mp 200°C.

Step 2): A mixture of 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide(2.4g, 5mmol) and Raney Ni in methanol (50ml) was hydrogenated at room temperature under stirring under 50 psi hydrogen pressure for 2 hours and then filtered. The filtrate was concentrated to give 2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide(2.2g, 100%).

PREPARATION 13

2-Amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

In a similar manner to that of Preparation 12, but replacing 4-aminomethyl-1-diphenylmethylpiperidine with 4-amino-1-diphenylmethylpiperidine(US Patent No. 4,267,318), 2-amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared.

PREPARATION 14

2-Amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide

In a similar manner to that of Preparation 12, 2-amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from 5-fluoro-2-nitrobenzoic acid and 4-amino-1-diphenylmethylpiperidine.

PREPARATION 15

2-Amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Step 1): In a similar manner to Preparation 12 Step 1), 3-chloro-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from 3-chloro-2-nitrobenzoic acid and 4-amino-1-diphenylmethylpiperidine.

Step 2): A solution of 3-chloro-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide (13.5g, 30mmol) and 40 % dimethylamine (20ml) in DMF (60ml) was heated at 130 °C for 15.5 hours in a sealed tube. The mixture was poured into water and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was recrystallized (ethyl acetate/ hexane) to give 3-dimethylamino-2-nitro-N-(1-diphenylmethyl piperidin-4-yl)benzamide (88.5%): mp 176 °C.

Step 3): In a similar manner to Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide with 3-dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide, 2-amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared.

PREPARATION 16

2-Amino-3,5-dimethoxy-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Step 1): A solution of $SOCl_2$ (0.5ml, 6.6mmol) in chloroform (10ml) was added dropwise to a solution of 3,5-dimethoxy-2-nitrobenzoic acid [ Bull. Soc. Chim. Fr., 127, 258 (1990)] (1.0g, 4.4mmol) and a catalytic amount of DMF in chloroform (20ml) at room temperature. The reaction mixture was refluxed for 1 hour and then concentrated. The residue was dissolved in THF(10ml). The THF solution was added dropwise to a solution of 4-amino-1-diphenylmethylpiperidine (1.2g, 4.4mmol) and triethylamine(0.5ml, 6.6mmol) in THF (20ml) at 5°C. The mixture was stirred at room temperature for 1 hour and then concentrated. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in dichloromethane) to give 3,5-dimethoxy-2-nitro-N-(1-diphenylmethyl-piperidin-4-yl)benzamide (81.0%): mp 148-150 °C.
Step 2): In a similar manner to that of Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)methylbenzamide with 3,5-dimethoxy-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide, 2-amino-3,5-dimethoxy -N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared: 100 %.

PREPARATION 17

2-Amino-N-(2,6-diisopropylphenyl)benzamide

Step 1): In a similar manner to that of Preparation 16 Step 1), 2-nitro-N-(2, 6-diisopropylphenyl)benzamide was prepared from 2-nitrobenzoyl chloride and 2,6-diisopropylaniline: 67.9%, mp 119-121 °C.
Step 2): Zinc powder (7.81 g, 119 mmol) was added slowly to a solution of 2-nitro-N-(2, 6-diisopropylphenyl)benzamide (2.0g, 6.3mmol) in acetic acid (38.3ml) below 10°C. The mixture was stirred for 2 hours at room temperature. The excess reagent was filtered off and the filtrate was neutralized with 10% NaOH solution. The mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The residue was recrystallized (ethyl acetate/ hexane) to give 2-amino-N-(2,6-diisopropylphenyl)benzamide (77.1 %): mp 207-209 °C.

PREPARATION 18

2-Amino-5-hydroxy-N-(3,3-diphenylpropyl)benzamide

In a similar manner to that of Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide with 5-benzyloxy-2-nitro-N-(3, 3-diphenylpropyl)benzamide [J. Med. Chem. 31, 2136 (1988)], 2-amino-5-hydroxy-N-(3, 3-diphenylpropyl)benzamide was prepared.

PREPARATION 19

2-Amino-N-(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and its analogue compounds of the formula(2).

A solution of 4-aminomethyl-1-diphenylmethylpiperidine (2.5g, 9.15mmol) in dichloromethane (10ml) was added to a suspension of isatoic anhydride (1.0g, 6.1mmol) in dichloromethane (25ml) at room temperature. The reaction mixture was stirred for 1 hour and then poured into chloroform and washed with 5% $NaHCO_3$ solution. The organic layer was concentrated. The residue was dissolved in dichloromethane (25ml) and poured into hexane (400ml) to give 2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide as precipitate (100%): mp 153-154 °C.
In a similar manner, but replacing the 4-aminomethyl-1-diphenylmethylpiperidine and the isatoic anhydride with other appropriately substituted amine and other appropriately substituted isatoic anhydride respectively, the following compounds were prepared and identified.

2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
2-amino-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
2-amino-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
2-amino-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide;

2-amino-N-(1-benzylpiperidin-4-yl)benzamide;
2-amino-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide;
2-amino-N-(pyridin-3-yl)benzamide;
2-amino-N-(pyridin-2-yl)benzamide;
1-(2-aminobenzoyl)-4-diphenylmethylpiperazine;
1-(2-aminobenzoyl)-4-(2-methoxyphenyl)piperazine;
1-(2-aminobenzoyl)-4-diphenylmethylhomopiperazine;
1-(2-aminobenzoyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine.

PREPARATION 20

2-Amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide

Step 1): To a cooled solution (0-5°C) of 4-aminometyl-1-diphenylmethylpiperidine (3.0g, 0.01 mol) in formic acid (7.5ml), acetic anhydride (6ml) was added and the reaction mixture was stirred at room temperature for 17 hours. An aqueous NaOH solution was added to adjust the mixture to pH 12 and the mixture was extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was recrystallized (diisopropyl ether) to give 4-(N-formylamino)methyl-1-diphenylmethylpiperidine (2.9g, 88%); mp 125°C.
Step 2): In a similar manner to that of Preparation 1 step2), 4-(N-formylamino)methyl-1-diphenylmethylpiperidine was reduced by $LiAlH_4$ to give 4-(N-methylamino)methyl-1-diphenylmethylpiperidine; yield 100%.
Step 3): A solution of 4-(N-methylamino)methyl-1-diphenylmethylpiperidine (1.8g, 6.0mmol), isatoic anhydride (0.9g, 5.5mmol) and 4-dimethylaminopyridine (0.74g) in DMF (25ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into 1 % $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate and hexane) to give 2-amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide(1.5g, 67%).

EXAMPLES

EXAMPLE 1

2-(N'-n-Heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

A solution of phenyl chloroformate (0.7ml, 5mmol) in dichloromethane (5ml) was added dropwise to a solution of 2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl) methyl]benzamide (2.2g, 5mmol) and $NaHCO_3$ (1.0g, 11.9mmol) in dichloromethane (50ml). The reaction mixture was stirred at 0 °C for 30 minutes and then poured into water and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated to give 2-phenoxy-carbonylamino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide.

n-Heptylamine (2.3g, 20.2mmol) was added to a solution of the carbamate described above in dichloromethane (50ml). The mixture was refluxed for 3 hours and then concentrated. The residue was purified by column chromatography on silica gel to give 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (1.8g, 62.0%): mp 178-179 °C; $^1H$ NMR (DMSO-$d_6$) 0.86 (3H, t), 1.14-1.47 (12H, m), 1.50-1.68 (3H, m), 1.79 (2H, t), 2.70-2.89 (8H, m), 2.97 (2H, dt), 3.14 (2H, t), 4.27 (1H, s), 6.78-6.90 (3H, m), 7.13-7.41 (10H, m), 7.85 (1H, d), 8.51 (1H, t), 9.17 (1H, s).

In a similar manner, the following compounds (Example 2 to 26) were prepared from other appropriately substituted 2-amino-benzamide and other appropriately substituted amine which were described in braces: {} after title of these compounds.

EXAMPLE 2

2-(N'-n-Butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-butylamine}: yield 80.2% ; mp 197-198°C;$^1H$ NMR (DMSO-$d_6$) 0.86 (3H, t), 1.24-1.83 (11H, m), 2.79 (2H, d),3.02(2H, dd), 3.15 (2H, t), 4.27 (1H, s), 6.91 (1H, t), 7.13-7.41 (12H, m), 7.57 (1H, d), 8.21 (1H, d), 8.57 (1H, t), 9.92 (1H, s).

EXAMPLE 3

2-(N'-n-Pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-pentylamine}:yield 29.9%; mp 178-180 °C (EtOH); $^1$H NMR (DMSO-$d_6$) 0.86 (3H, t), 1.24-1.83 (13H, m), 2.79 (2H, d), 2.96 (2H, dd), 3.15 (2H, t, ), 4.26 (1H, s), 6.91 (1H, t), 7.13-7.41 (12H, m), 7.57 (1H, d), 8.22 (1H, d), 8.58 (1H, t), 9.93 (1H, s).

EXAMPLE 4

2-(N'-n-Hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-hexylamine}: yield 56.9% ; mp 168-169 °C (EtOH); $^1$H NMR (DMSO-$d_6$) 0.86 (3H, t), 1.25-1.83 (15H, m), 2.79 (2H,d), 3.01 (2H, dd), 3.17 (2H, t), 4.26 (1H, s), 6.91 (1H, t), 7.13-7.40 (12H, m), 7.57 (1H, d), 8.21 (1H, d), 8.57 (1H, t), 9.95 (1H, s).

EXAMPLE 5

2-(N'-n-Heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine}: yield 67%; mp 146-148 °C $^1$H NMR (DMSO-$d_6$) 0.86 (3H, t), 3.00 (2H, dd), 3.15 (2H, m), 4.27 (1H, s), 6.89-7.58 (14H, m), 8.04 (1H, d), 8.19 (1H, q), 8.59 (1H, t), 9.93 (1H, s).

EXAMPLE 6

2-(N'-n-Octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-octylamine}: yield 72.1%; mp 155-157 °C (EtOH); $^1$H NMR (DMSO-$d_6$) 0.86 (3H, t), 1.25-1.83 (19H, m), 2.79 (2H,d), 3.01 (2H, dd), 3.15 (2H, t), 4.26 (1H, s), 6.91 (1H, t), 7.13-7.41 (12H, m), 7.57 (1H, d), 8.21 (1H, d), 8.58 (1H, t), 9.95 (1H, s).

EXAMPLE 7

2-(N'-n-Butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-butylamine}: yield 93.0%; mp 204-206 °C; $^1$H NMR ($CDCl_3$) 0.92 (3H, t), 1.23-1.67 (6H, m), 2.04 (4H, m), 2,84 (2H,m), 3.24 (2H, q), 4.11 (1H, m), 4.28 (1H, s), 4.53 (1H, t), 6.55 (1H, d), 6.94 (1H, dd), 7.15-7.44 (12H, m), 8.40 (1H, d), 10.26 (1H, s).

EXAMPLE 8

2-(N'-n-Pentylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-pentylamine}: yield 65.0%; mp 199-201°C; $^1$H NMR ($CDCl_3$) 0.89 (3H, t), 1.29-1.70 (8H, m), 1.92-2.15 (4H, m), 2.79-2.88 (2H, m), 3.23 (2H, q), 3.87-4.05 (1H, m), 4.28 (1H, s), 4.56 (1H, t), 6.08(1H, d), 6.91-7.44 (13H, m), 8.41 (1H, d), 10.25 (1H, s).

EXAMPLE 9

2-(N'-n-Hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-hexylamine}: yield 52.0%; mp 192-194 °C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 1.25-1.67 (10H, m), 1.92-2.13 (4H, m), 2.79-2.87(2H, m), 3.24 (2H, q), 3.88-4.02 (1H, m), 4.28 (1H, s), 4.54 (1H, t), 6.05 (1H, d), 6.91-7.46 (13H, m), 8.41 (1H, d), 10.27 (1H, s).

EXAMPLE 10

2-(N'-n-Octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octylamine}: yield 51.0%; mp 149-151 °C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 1.23-1.68 (14H, m), 1.92-2.15 (4H, m), 2.80-2.88(2H, m), 3.23 (2H, q), 3.86-4.02 (1H, m), 4.28 (1H, s), 4.57 (1H, t), 6.06 (1H, d), 6.91-7.48 (13H, m), 8.41 (1H, d), 10.26 (1H, s).

EXAMPLE 11

2-(N'-n-Nonylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-nonylamine}: yield 94.0%; mp 149-150 °C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 1.25 (12H, m), 1.56 (6H, m), 2.04 (4H, m), 2.84 (2H, m), 3.23 (2H, q), 3.91 (1H, m), 4.28 (1H, s), 4.54 (1H, t), 6.05 (1H, d), 6.94 (1H, dd), 7.15-7.44 (12H, m), 8.40 (1H, d), 10.26 (1H, s).

EXAMPLE 12

2-(N'-n-Decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-decylamine}: yield 83.0%; mp 204-206 °C; $^1$H NMR ($CDCl_3$) 0.92 (3H, t), 1.23-1.67 (6H, m), 2.04 (4H, m), 2,84 (2H,m), 3.24 (2H, q), 4.11 (1H, m), 4.28 (1H, s), 4.53 (1H, t), 6.55 (1H, d), 6.94 (1H, dd), 7.15-7.44 (12H, m), 8.40 (1H, d). 10.26 (1H, s).

EXAMPLE 13

3,5-Dimethoxy-2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-3,5-dimethoxy-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine} : yield 64.0%; mp 195-198 °C; $^1$H NMR ($CDCl_3$) 0.85 (3H, t), 2.78 (2H, d), 3.18 (2H, dd), 3.76 (3H, s), 3.81 (3H, s), 3.95 (1H,m), 4.23 (1H, s), 4.86 (1H, t), 5.89 (1H, s), 6.48 (1H, d), 6.84 (1H, d), 7.35 (1H, d).

EXAMPLE 14

5-Fluoro-2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine}: yield 67% ; mp 208-210 °C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 2.58 (2H, d), 3.22 (2H, dd), 3.90 (1H, m),4.23 (1H, s), 4.52 (1H, t), 5.05 (1H, d), 8.34 (1H, q), 9.94 (1H, s).

EXAMPLE 15

2-(N'-n-Heptylureido)-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine}: yield 71.2%; mp209-212°C; $^1$H NMR (DMSO-$d_6$) 0.84 (3H, t), 1.21 (6H, d) 3.02 (2H, q), 3.10(1H, m), 3.69 (1H, m), 4.29 (1H, s), 6.50 (1H, t), 7.14-7.42 (13H, m), 7.66 (1H, s), 8.03 (1H, d).

EXAMPLE 16

2-(N'-n-Heptylureido)-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-5-nitry-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine}: yield 52.0%; mp 165-166 °C; $^1$H NMR ($CDCl_3$) 0.86 (3H, t), 1.27-1.96 (12H, m), 2.02 (4H, m), 2.89 (2H, q), 3.24 (2H, q), 3.92 (1H, m), 4.30 (1H, s), 4.76 (1H, t), 6.33 (1H, d), 7.16-7.42 (10H, m), 8.25 (1H, dd), 8.30 (1H, d), 8.67 (1H, d), 10.86 (1H, s).

EXAMPLE 17

2-(N'-n-Heptylureido)-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide

{2-amino-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide and n-heptylamine}: yield 76.1%; mp 109-111 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.24-1.62 (15H, m), 1.92-2.08 (2H, m), 2.10-2.24 (1H, m), 2.31-2.43 (1H, m), 2.52-2.63 (1H, m), 2.71 (1H, dd), 3.24 (1H, dt), 3.37 (2H, dt), 4.16 (1H, s), 4.64 (1H, t), 6.22 (1H, t), 6.92 (1H, dd), 7.10-7.50 (12H, m), 8.41 (1H, d), 10.26 (1H, s).

EXAMPLE 18

2-(N'-n-Heptylureido)-N-(2,6-diisopropylphenyl)benzamide

{2-amino-N-(2,6-diisopropylphenyl)benzamide and n-heptylamine}: yield 63.2%; mp 123-125°C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.16-1.30 (20H, m), 1.45-1.51 (2H, m), 3.07-3.25 (4H, m)4.59-4.63 (1H, t), 7.04-7.10 (1H, m), 7.25-7.71 (6H, m), 8.52-8.55 (1H, d), 10.36 (1H, s).

EXAMPLE 19

2-(N'-n-Heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide

{2-amino-5-hydroxy-N-(3,3-diphenylpropyl)benzamide and n-heptylamine}: yield 81.3%; mp 161.0-161.5 °C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 1.26 (8H, t), 1.39-1.55 (2H, m), 2.32 (2H,dt), 3.17 (2H, dt), 3.30 (2H, dt), 3.96 (1H, t), 4.69 (1H, t), 6.46 (1H, t), 6.58 (1H, d), 6.71 (1H, dd), 7.04 (1H, s), 7.13-7.30 (10H, m), 7.75 (1H, d), 9.41 (1H, s).

EXAMPLE 20

2-[N'-(3,5-Di-t-butyl-4-hydroxyphenyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 4-amino-2,6-di-t-butylphenol [G. M. Coppinger, Tetrahedron 18, 61 (1962)]}: yield 27.0%; mp 218-225 °C; $^1$H NMR ($CDCl_3$) 1.43 (18H, m), 1.55-1.64 (2H, m), 1.89-2.13 (2H, m), 3.90-3.98 (1H, m), 4.37 (1H, s), 5.07 (1H, s), 5.43 (1H, d), 6.33 (1H, s), 6.95 (1H, t), 7.16-7.46 (14H, m), 8.43 (1H, d), 10.35 (1H, s).

EXAMPLE 21

2-[N'-(4-n-Heptylphenyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 4-heptylaniline}: yield 86.0%; mp 173-175 °C; $^1$H NMR ($COCl_3$) 0.87 (3H, t), 1.28 (6H, m), 1.58 (6H, m), 2.01 (4H, m), 2.25 (2H, t), 2.83 (2H, m), 3.88 (1H, bs), 4.26 (1H, s), 6.07 (1H, d), 6.54 (1H, s), 6.90-7.43 (18H, m), 8.37 (1H, d), 10.41 (1H, s).

EXAMPLE 22

2-[N'-(2-t-Butoxycarbonylaminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and t-butyl N-(2-aminoethyl) carbamate}: yield 89.0%; mp 226-228 °C; $^1$H NMR ($CDCl_3$) 1.41 (9H, s), 1.63 (2H, m), 1.94-2.12 (4H, m), 2.84 (2H, m), 3.33 (4H, m), 3.92 (1H, m), 4.28 (1H, s), 4.97 (2H, m), 6.10 (1H, d), 6.96 (1H, t), 7.25 (12H, m), 8.36 (1H, d) 10.29 (1H, s).

EXAMPLE 23

1-[2-(N'-n-Heptylureido)benzoyl]-4-(2-methoxyphenyl)piperazine

{1-(2-aminobenzoyl)-4-(2-methoxyphenyl)piperazine and n-heptylamine}: yield 64.0%; mp 209-212 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 3.19 (2H, q), 3.87 (3H, s), 4.96 (1H, m), 3.69 (1H,m), 4.29 (1H, t), 6.87-7.39 (7H, m), 8.04 (1H, d), 8.09 (1H, d).

EXAMPLE 24

1-[2-(N'-n-Heptylureido)benzoyl]-4-diphenylmethylpiperazine

{1-(2-aminobenzoyl)-4-diphenylmethylpiperazine and n-heptylamine}: yield 86.0%; mp 125-127 °C; $^1$H NMR ($CDCl_3$) 0.89 (3H, t), 1.29-1.31 (8H, m), 1.47-1.49 (2H, m), 2.32-2.50 (4H,m), 3.19 (2H, q), 3.41-3.80 (4H, m), 4.23 (1H, s), 3.90 (1H, t), 6.93 (1H, t), 7.09-7.41 (12H, m), 8.01 (1H, s), 8.04 (1H, d).

EXAMPLE 25

2-[N'-(2-Aminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 1,2-diaminoethane}: yield 90.0 %; $^1$H NMR ($CDCl_3$) 1.58-2.07 (6H,m), 2.83 (4H, m), 3.25 (2H, m), 3.87 (1H, s), 4.25 (1H, s), 5.70 (1H, s), 6.45.(1H, d), 6.92 (1H, t), 7.14-7.4 (12H, m), 8.30 (1H, d), 10.11 (1H, s).

EXAMPLE 26

2-[N'-(2-Aminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and 1,2-diaminoethane}: yeild 97%; mp 101-103 °C; $^1$H NMR ($CDCl_3$) 1.34-1.43 (2H, m), 1.54-1.68 (3H, m), 1.83 (2H, t), 2.81-2.92 (6H, m), 3.27-3.31 (4H, m), 4.24 (1H, s), 5.31 (1H, bt), 6.39 (1H, bt), 6.82 (1H, d), 7.10-7.42 (12H, m), 8.33 (1H, d, J=8.2Hz), 10.20 (1H, s).

EXAMPLE 27

2-(N'-n-Heptylureido)-N-(1-phenoxylcarbonylpiperidin-4-yl)benzamide

Phenyl chloroformate (5.0ml, 40mmol) was added to a solution of 2-amino-N-(1-benzylpiperidin-4-yl)benzamide (3.1g, 10mmol) in chloroform (50ml). The mixture was refluxed for 2 hours. After cooling, ether was added and then the solution was washed with saturated $NaHCO_3$ solution and brine. The organic layer was concentrated to give 2-phenoxy carbonylamino-N-(1-phenoxylcarbonylpiperidin-4-yl)benzamide.

A solution of 2-phenoxycarbonylamino-N-(1-phenoxylcarbonylpiperidin-4-yl)benzamide (1.6g, 3.5mmol) and n-heptylamine (0.45g, 3.9mmol) in toluene (20ml) was refluxed for 4 hours and then concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in petroleum ether) to give 2-(N'-n-heptylureido)-N-(1-phenoxy carbonylpiperidin-4-yl)benzamide: yield 95.0%; mp 142-144 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t) 1.28-1.33 (7H, m), 19-1.62 (4H, m), 2.05-2.17 (2H, m), 3.04-3.19 (2H, m), 3.25 (2H, q), 4.10-4.15 (1H, m), 4.24-4.40 (2H, m), 4.59 (1H, t), 6.35 (1H, d), 6.92 (1H, t), 6.97-7.44 (8H, m), 8.40 (1H, d), 10.20 (1H, s).

EXAMPLE 28

2-(N'-n-Heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide

A solution of octanoic acid (0.5g, 3.5mmol), diphenylphosphoryl azide(1.0g, 3.6mmol) and $Et_3N$ (0.4g, 4mmol)in acetonitrile (10ml) was refluxed for 1 hour and then concentrated. The residue was dissolved in chloroform (10ml). 2-Amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide (0.74g, 1.79mmol) was added to the solution. The mixture was refluxed for 50 hours and then concentrated. The residue was purified by column chromatography on silica gel (10 % to 30% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide(0.88 g, 88.9 %): mp 125-127 °C $^1$H NMR($CDCl_3$) 0.88 (3H, t), 1.09-1.43 (10H, m), 1.44-1.77 (7H, m), 1.78-1.93 (2H,m), 2.88 (2H, d), 3.24 (2H, dt), 3.42 (2H, dt), 4.23 (1H, s), 4.58 (1H, t), 6.16 (1H, t), 6.93 (1H, t), 7.13-7.45 (12H, m), 8.41 (1H, d), 10.28 (1H, s).

In a similar manner, the following compounds (Example 29 to 42) were prepared from other appropriately substituted 2-amino-benzamide and other appropriately substituted carboxylic acid which were described in braces: {} after titles of these compounds.

EXAMPLE 29

2-(N'-n-Pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide

{2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide and n-hexanoic acid}: yield 40.6%; mp 124-127 °C; $^1$H NMR ($CDCl_3$) 0.90 (3H, t), 1.25-1.44 (6H, m), 1.47-1.61 (5H,m), 1.61-1.71(2H, m), 1.83 (2H, t), 2.88 (2H, d), 3.27 (2H, dt), 3.45 (2H, dt), 4.23 (1H, s), 4.60 (1H, t), 6.15 (1H, t), 6.56 (1H, t), 7.13-7.44 (12H, m), 8.41 (1H, d), 10.28 (1H, s).

EXAMPLE 30

2-(N'-n-Hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide

{2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide and n-heptanoic acid}: yield 91.3%; mp 143-144 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.22-1.46 (8H, m), 1.46-1.75 (7H,m), 1.83 (2H, t), 2.88 (2H, d), 3.24 (2H, dt), 3.42 (2H, dt), 4.23 (1H, s), 4.58 (1H, t), 6.17 (1H, t), 6.93 (1H, t), 7.13-7.44 (12H, m), 8.40 (1H, d), 10.24 (1H, s).

EXAMPLE 31

2-(N'-n-Heptylureido)-5-dimethylamino-N-(1-diphenylmethypiperdin-4-yl)benzamide

{2-amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid}: yield 70.0%; mp 204-206 °C; $^1$H NMR ($CDCl_3$) 0.86 (3H, t), 2.86 (6H, m), 3.76 (1H, m),4.30 (1H, s), 6.81-7.84 (3H, m), 7.15-7.44 (10H, m), 8.35 (1H, d), 9.08 (1H, s).

EXAMPLE 32

2-(N'-n-Heptylureido)-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid} : yield 38.0%; mp 203 °C; $^1$H NMR ($CDCl_3$) 0.85 (3H, t), 1.12-1.34 (8H, m), 1.35-1.61 (4H,m),1.92(2H, d), 2.03 (2H, t), 2.55 (6H, s), 2.80 (2H, d), 3.16 (2H, dt), 3.86-4.05 (1H, m), 4.24 (1H, s), 5.56 (1H, d), 6.66 (1H, d), 6.93 (1H, s), 7.09-7.41 (13H, m).

EXAMPLE 33

2-(N'-n-Heptylureido)-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-octanoic acid}: yield 68.0%; mp 140°C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.24-1.78 (19H, m), 2.93 (3H,s), 2.85-3.20 (5H, m), 3.42 (1H, d), 4.21 (1H, s), 5.07 (1H, t), 6.98-7.36 (14H, m), 7.98 (1H, s).

EXAMPLE 34

2-(N'-n-Heptylureido)-N-(pyridin-3-yl)benzamide

{2-amino-N-(pyridin-3-yl)benzamide and n-octanoic acid}: yield 85.2%; mp 144.5 °C; $^1$H NMR($CDCl_3$) 0.85 (3H, t), 1.10-1.34 (8H, m), 1.35-1.49 (2H, m), 3.03 (2H, q), 7.05 (1H, t),7.21 (1H, bt), 7.38-7.48 (2H, m), 7.72 (1H, d), 8.09-8.14 (1H, m), 8.22 (1H, d), 8.32-8.35 (1H, m), 8.90 (1H, t), 9.24 (1H, s), 10.57 (1H, s).

EXAMPLE 35

2-(N'-n-Heptylureido)-N-(pyridin-2-yl)benzamide

{2-amino-N-(pyridin-2-yl)benzamide and n-octanoic acid}: yield 84.0%; mp 118.5 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.18-1.40 (8H, m), 1.44-1.62 (2H, m), 3.27 (2H, q), 4.66 (1H, t),6.99-7.11 (2H, m), 7.49 (1H, t), 7.63 (1H, d), 7.76 (1H, t), 8.24 (1H, d), 8.29-8.33 (1H, m), 8.49 (1H, d), 8.68 (1H, s), 10.11 (1H, s).

EXAMPLE 36

2-[N'-(1,1-Dimethyltridecyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 2,2-dimethyl tetradecanoic acid}: yield 38.0%; mp 146-148 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.24-1.32 (22H, m), 1.55 (6H, s), 1.62-1.66 (2H, m), 1.96-2.12 (4H, m), 2.83-2.87 (2H, m), 3.87-3.94(1H,m), 4.28 (1H, s), 4.44 (1H, t), 6.08 (1H, d), 6.89-6.95 (1H, t), 7.16-7.42 (12H, m),8.37(1H, d) 10.04 (1H, s).

EXAMPLE 37

2-[N'-(2,6-Diisopropylphenyl)ureido]-N-(1-diphenylmethypiperdn-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 2,6-diisopropyl benzoic acid}: yield 63.0%; mp 118 °C; $^1$H NMR ($CDCl_3$) 1.17 (12H, d), 1.43-1.49 (2H, m), 1.816 (2H,m), 1.96-2.04 (2H, m), 2.77-2.81 (2H, m), 3.23-3.33 (2H, m), 3.75 (1H, m), 4.25 (1H, s), 5.82-5.91 (2H, m), 6.95 (1H, t), 7.16-7.41 (15H, m), 8.43 (1H, d), 9.53-9.54 (1H, m).

EXAMPLE 38

1-[2-(N'-n-Heptylureido)benzoyl]-4-diphenylmethylhomopiperazine

{1-(2-aminobenzoyl)-4-diphenylmethylhomopiperazine and n-octanoic acid}: yield 82.0%; mp 125 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.29 (8H, bs), 1.42-1.56 (2H, s), 1.65-1.78 (1H, m),1.83-1.95 (4H, m), 2.51-2.82 (4H, m), 3.13-3.28 (1H, m), 3.35-3.61 (2H, m), 3.67-3.88 (2H, m), 4.56 (1H, d), 4.85-5.00 (1H, m), 6.98 (1H, dt), 7.09-7.49 (12H, m), 7.82-8.16 (2H, m).

EXAMPLE 39

1-[2-(N'-n-Heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine

{1-(2-aminobenzoyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine and n-octanoic acid}: yield 39.0%; mp 144 °C; $^1$H NMR ($CDCl_3$) 0.89 (3H, t), 1.18-1.43 (8H, m), 1.44-1.63 (2H,m), 2.18-2.48 (4H, m), 2.77-2.88 (2H, m), 3.22 (2H, q), 3.26-3.93 (4H, m), 3.94-4.02 (3H, m), 4.67 (1H, t), 6.92 (1H, t), 7.04-7.35 (10H, m), 8.07 (2H, t).

EXAMPLE 40

2-(N'-n-Heptylureido)-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide

{2-amino-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide and n-octanoic acid}: yield 45.3%;mp 123-124.5°C (AcOEt/hexane); $^1$H NMR ($CDCl_3$) 0.88 (3H,t), 1.14-1.40 (13H,m),1.45-1.66 (6H,m), 1.81 (2H, t), 2.87 (2H, d) 3.24 (1H, dt), 3.38 (2H, dt), 4.22 (1H, s), 4.60 (1H, t), 6.24 (1H, t), 6.93 (1H, t), 7.13-7.32 (7H, m), 7.34-7.44 (5H, m), 8.40 (1H, d), 10.28 (1H, s).

EXAMPLE 41

N-(1-Benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide

{2-amino-N-(1-benzylpiperidin-4-yl)benzamide and n-octanoic acid}: yield 48.4%; mp 134 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H,t), 1.20-1.40 (8H,m), 1.45-1.69 (4H,d), 2.18 (2H,t), 2.86 (2H,d), 3.24 (2H,q), 3.25 (2H, s), 3.83-4.03 (1H, m), 4.62 (1H,t), 6.13 (1H,d), 6.94 (1H,dt), 7.24-7.43 (7H,m), 8.40 (1H,dd), 10.26 (1H,s).

EXAMPLE 42

N-(1-Benzylpiperidin-4-yl)-2-(N'-n-octylureido)benzamide

{2-amino-N-(1-benzylpiperidin-4-yl)benzamide and n-nonanoic acid}: yield 81.9%; mp 129 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H,t), 1.17-1.41 (10H,m), 2.00 (2H,d), 2.18 (2H,t), 2.86 (2H,d),3.25(2H,q), 3.52 (2H,s), 3.83-4.02 (1H,m), 4.56 (1H,t), 6.06 (1H,d), 6.95 (1H, dt), 7.24-7.45 (7H,m), 8.42 (1H,dd), 10.29 (1H,s).

EXAMPLE 43

N-[1-[2,6-Diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-heptylureido)benzamide

Step 1): 10% Pd/C was added to a solution of the N-(1-benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide (1.4g, 3.1 mmol) obtained in Example 41 in methanol (25ml) under nitrogen. The mixture was shaken under 50 psi hydrogen pressure for 5 hours, and then filtered under nitrogen. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (50 % methanol and 0.8% $NH_4OH$ in dichloromethane) to give N-(piperidin-4-yl)-2-(N'-n-heptylureido)benzamide: 48.4%; mp 159 °C.

Step 2): N-(Piperidin-4-yl)-2-(N'-n-heptylureido)benzamide (0.96g, 2.7mmol) and $NaBH_3CN$ (0.17g, 2.7mmol) were added into a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-3-formyl-5-methoxymethylpyridine (0.9g, 2.7mmol) in MeOH (30ml). The mixture was stirred at room temperature for 72 hours, and then water was added at 0°C, extracted with dichloromethane, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (10 to 50 % ethyl acetate in hexane) to give N-[1-[2,6-diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-heptylureido)benzamide (0.65 g, 35.7%): mp 123 °C $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.17-1.46 (22H, m), 1.49-1.66 (2H, m), 1.80-2.00 (4H, m), 2.57 (2H, d), 3.09-3.53 (9H, m), 3.68-3.89 (1H, m), 3.49 (2H, s), 4.53 (1H, t), 5.98 (1H, d), 6.93 (1H, t), 7.05-7.24 (4H, m), 7.33-7.48 (2H, m), 8.41 (1H, d), 10.30 (1H, s).

The following compound (Example44) was prepared in a similar manner, but replacing N-(1-benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide with N-(1-benzylpiperidin-4-yl)-2-(N'-n-octylureido)benzamide.

EXAMPLE 44

N-[1-[2,6-Diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-octylureido)benzamide

Yield 34.1%; mp 132 °C; $^1$ NMR ($CDCl_3$) 0.88 (3H, t), 1.17-1.46 (24H, m), 1.49-1.66 (2H, m),1.80-2.00 (4H, m), 2.57 (2H, d), 3.09-3.55 (9H, m), 3.68-3.89 (1H, m), 3.49 (2H, s), 4.53 (1H, t), 5.98 (1H, d), 6.93 (1H, t), 7.05-7.24 (4H, m), 7.33-7.48 (2H, m), 8.41 (1H, d), 10.30 (1H, s).

EXAMPLE 45

2-(N'-n-Heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

A mixture of 2-n-heptylamino-4H-3,1-benzoxazin-4-one (3.0g, 10mmol) and 4-amino-1-diphenylmethylpiperidine (3.0g, 10mmol) in toluene (20ml) was refluxed for 3 hours and then concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide (2.3 g, 40%): mp 182°C; $^1$H NMR ($CDCl_3$) 0.87 (3H, t), 1.27-1.30 (8H, m), 1.47-1.67 (4H, m), 1.95-2.12 (4H, m), 2.84 (2H, d), 3.24 (2H, q), 3.90-3.94 (1H, m), 4.26 (1H, s), 4.56 (1H, t), 6.09 (1H, d), 6.92-6.98 (1H, m), 7.16-7.44 (12H, m), 8.41 (1H, d), 10.26 (1H, s).

In a similar manner, the following compounds (Example46 to 53) were prepared from 2-n-heptylamin-4H-3,1-benzoxadin-4-one and other appropriately substituted amines which were described in braces: {} after titles of these compounds.

EXAMPLE 46

N-(3,5-Di-t-butyl-4-hydroxyphenyl)-2-(N'-n-heptylureido)benzamide

{4-amino-2,6-t-butylphenol}: yield 22.0%; mp 211-214 °C; $^1$H NMR ($CDCl_3$) 0.86 (3H, d), 1.27-1.51 (28H, m), 3.16-3.23 (2H, q), 5.34 (1H, s), 5.60 (1H, s), 6.97 (1H, d) 7.00-7.45 (4H, m), 7.64 (1H, d), 8.34 (1H, d), 9.17 (1H, s), 9.84 (1H, s).

EXAMPLE 47

N-(4-n-Heptylphenyl)-2-(N'-n-heptylureido)benzamide

{4-n-heptylaniline}: yield 40.0%; mp 155-157 °C; $^1$H NMR ($CDCl_3$) 0.85-0.94 (6H, d), 1.28-1.32 (20H, m), 2.61 (2H, t), 3.25 (2H, q), 4.61 (1H, s), 6.94-7.03 (1H, m), 7.19-7.65 (6H, m), 8.00 (1H, s), 8.40 (1H, d), 10.01 (1H, s).

EXAMPLE 48

N-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)benzamide

{11-aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin}:yield 60.0%; mp 71-76 °C; $^1$H NMR($CDCl_3$) 0.88 (3H, t), 1.32-1.62 (8H, m), 3.23-3.30 (2H, m), 4.77 and 5.69 (2H, q), 6.39(1H, s), 6.90-7.43 (10H, m), 8.40 (1H, d), 10.21 (1H, d). EXAMPLE 49

N-[1-[2-(4,5-Diphenylimidazol-2-yl)thioethyl]piperidin-4-yl]-2-(N'-n-heptylureido)benzamide

{2-[2-(4-aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole}: yield 45.6%; mp 160-161 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H, t), 1.08 (3H, ddd), 1.28-1.31 (8H, m), 1.51-1.56 (2H, m), 1.80(2H, d) 2.16 (2H, t), 2.93 (2H, t), 3.08-3.04 (4H, m), 3.24 (2H, dt), 3.80 (1H, m), 4.63 (1H, t), 5.27 (1H, d) 7.02-7.54 (13H, m), 8.43 (1H, d) 10.10 (1H, s).

EXAMPLE 50

N-(3,3-Diphenylpropyl)-2(N'-n-heptylureido)benzamide

{3,3-diphenylpropylamine}: yield 60.0%; mp 118 °C; $^1$H NMR ($CDCl_3$) 0.88 (3H,t), 1.06-1.72(10H,b), 2.38 (2H,q), 3.00-3.60 (4H,m), 4.00 (1H,t), 4.60(1H,t), 6.13 (1H,b), 6.64-7.52 (13H,m), 8.73 (1H,d), 10.28 (1H,s).

EXAMPLE 51

N-[1-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)piperidin-4-yl]-2-(N'-n-heptylureido)benzamide

{11-(4-aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin}: yield 54.1%; mp 198-199 °C; $^1$H NMR ($CDCl_3$) 0.82-0.93 (3H, m), 1.27-1.64 (12H, m), 1.93-1.95 (2H, m),2.12 (2H, q), 2.70 (1H, d), 2.87 (1H, d), 3.24 (2H, q), 3.90-4.00 (2H, m), 4.57 (2H, t), 6.03 (1H, d), 6.77-6.96 (4H, m), 7.09-7.45 (9H, m), 8.40 (1H, d), 10.26 (1H, s).

EXAMPLE 52

N-[2-(4,5-Diphenylimidazol-2-yl)thioethyl]-2-(N'-n-heptylureido)benzamide

{2-(2-aminoethylthio)-4,5-diphenylimidazole}: yield 35.9%; mp 285-288 °C; $^1$H NMR ($CDCl_3$) 0.97 (3H, t), 1.17-1.86 (10H, m), 3.24-3.31 (2H, m), 3.43 (2H, t), 3.86-3.92 (2H, m), 4.62-4.66 (1H, m), 6.36 (1H, t), 7.18-7.70 (13H, m), 8.36 (1H, d) 8.71-8.74 (1H, m), 10.53 (1H, s).

EXAMPLE 53

N-[2-(4,5-Diphenylimidazol-1-yl)ethyl]-2-(N'-n-heptylureido)benzamide

{1-(2-aminobenzoyl)-4-diphenylmethylpiperazine}: yield 86.0%; mp 169.7 °C; $^1$H NMR ($CDCl_3$)0.89 (3H, t), 1.18-1.59 (10H, m), 3.20-3.7 (2H, dt), 3.45-3.51 (2H, dt), 4.06 (2H, t), 5.09-5.15 (1H, m), 6.45 (1H, t), 6.88-6.93 (1H, m), 7.15-7.46 (12H, m), 7.59 (1H, s), 8.45 (1H, d), 9.69-9.70 (1H, m).

EXAMPLE 54

2-(N'-n-Heptylureido)-N-(1-diphenylmethylpiperidin-3-yl)benzamide

Step 1): A mixture of 2-(N'-n-heptylureido)-N-(pyridin-3-yl)benzamide obtained in the Example 34 (5.0g, 14mmol) and $PtO_2$ in acetic acid (70ml) was stirred at 40 °C under hydrogen atmosphere (50 psi) for 17 hours and then filtered. The filtrate was neutralized with 30% NaOH solution, extracted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (20% methanol and 0.8% $NH_4OH$ in dichloromethane) to give 2-(N'-n-heptylureido)-N-(piperidin-3-yl)benzamide (83.8%): mp 165 °C.

Step 2): Bromodiphenylmethane (1.4g, 5.6mmol) was added to a solution of 2-(N'-n-heptylureido)-N-(piperidin-3-yl)benzamide (1.0g, 2.8mmol) and $K_2CO_3$ (0.4g, 2.9mmol) in DMSO (5ml) at 0 °C. The mixture was refluxed for 18 hours, poured into 1% $NaHCO_3$ solution, extracted with ethyl acetate and washed with 1% $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica

gel (25% to 50% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-3-yl)benzamide (0.3g, 20.5%): mp 112 °C, 1H NMR ($CDCl_3$) 0.88 (3H, t), 1.23-1.35 (8H, m), 1.47-1.85 (6H, m), 2.05-2.20 (1H, m), 2.35-2.49 (1H, m), 2.57-2.80 (2H, m), 3.24 (2H, q), 4.12-4.23 (1H, m), 4.35 (1H, s), 4.57-4.65 (1H, m), 6.90-7.55 (14H, m), 8.48 (1H, d), 10.37 (1H, s).

EXAMPLE 55

2-(N'-n-Heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl) benzamide

In a similar manner to that of the Example 54 step 1), but replacing 2-(N'-n-heptylureido)-N-(pyridin-3-yl)benzamide with 2-(N'-n-heptylureido)-5-nitro-N-(1-diphenylmethyl piperidin-4-yl)benzamide, 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared.: yield 84.0%; mp 190-192 °C; $^1H$ NMR ($CDCl_3$) 0.84 (3H, t),1.26 (8H, m), 1.53 (8H, m), 1.92-2.11 (4H, m), 2.82 (2H, m), 3.19 (2H, td), 3.55 (2H,m), 3.91 (1H, s), 4.27 (1H, s), 4.46 (1H, m), 6.08 (1H, d), 6.71 (1H, d), 6.78 (1H, dd),7.15-7.41 (10H, m), 8.00 (1H, d), 9.27 (1H, s).

EXAMPLE 56

2-(N'-n-Heptylureido)-5-methylsulfonylamino-N-(1-diphenymethylpiperidin-4-yl)benzamide

Methanesulfonyl chloride (0.05ml, 0.65mmol) was added dropwise to a solution of triethylamine (0.09ml, 0.6mmol) and 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.32g, 0.59mmol) in dichloromethane (15ml) at 0 °C. The mixture was stirred for 24 hours and then concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in cyclohexane) to give 2-(N'-n-heptylureido)-5-methylsulfonylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.29g, 79.0%): mp 180-182 °C; $^1H$ NMR ($CDCl_3$) 0.85 (3H, t), 1.28 (4H, m), 1.57 (6H, m), 2.00 (4H, m),2.85 (2H, m), 2.95 (3H, s), 3.12 (2H, td), 3.90 (1H, m), 4.29 (1H, s), 4.63 (1H, m), 6.22 (1H, d), 6.46 (1H, d), 7.15-7.41 (12H, m), 8.36 (1H, d), 10.17 (1H, s).

EXAMPLE 57

2-(N'-n-Heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Triethylamine (0.098ml, 0.65mmol) and acetic anhydride (0.067ml, 0.07mmol) were added to a solution of the 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.32g, 0.59mmol) in dichloromethane (3ml) at room temperature. The mixture was stirred for 24 hours and then concentrated. The residue was purified by column chromatograpny on silica gel (50% ethyl acetate in cyclohexane) to give 2-(N'-n-heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.33g, 96.0%): mp. 113-115 °C, $^1H$ NMR ($CDCl_3$) 0.86 (3H, t), 1.27 (8H, m), 1.49-1.69 (4H, m), 1.92-2.08 (4H, m), 2.17 (3H, s), 2.85 (2H, m), 3.22 (2H, q), 3.90 (1H, m), 4.28 (1H, s), 4.57 (1H, t), 6.40 (1H, d), 7.03 (1H, dd), 7.15-7.40 (11H, m), 8.06 (1H, d), 8.30 (1H, d), 10.10 (1H, s).

EXAMPLE 58

2-(N'-n-Heptylureido)-5-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

In a similar manner to that of Example 28, 2-(N'-n-heptylureido)-5-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from n-pentanoic acic and 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide: yield 79.0%; mp 209-211 °C; $^1H$ NMR (DMSO-$d_6$) 0.83 (3H, t), 0.89 (3H, t), 3.77 (1H, m), 4.29 (1H, s), 6.08(1H, t), 7.00 (1H, bs), 7.15-7.40 (1H, m), 7.91 (1H, d), 8.30 (1H, s), 8.41 (1H, d), 9.06 (1H, d).

EXAMPLE 59

2-[N'-(2-Di-n-butylaminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

To a solution of the 1, 2-[N'-(2-aminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.33g, 0.7mmol) obtain in Example 25 and n-butyraldehyde (0.13ml, 1.44mmol) in methanol (5ml) was added by portions $NaBH_3CN$ (0.32g, 5.1mmol) under stirring and the pH was adjusted at 6 by adding acetic acid. Then the reaction mixture was stirred at room temperature for 2 hours. A few drops of concentrated HCl were added in order to decompose the excess of reducing reagent. The mixture was concentrated. The residue was dissolved in dichloromethane, then basified to pH 10 with 10 % NaOH solution and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give 2-[N'-(2-di-n-butylami-

noethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.15 g, 35.0 %): mp 159-161 °C; $^1$H NMR ($CDCl_3$) 0.89 (6H, t), 2.10 (4H, m), 2.48 (4H, t), 2.64 (2H, m), 3.84 (2H, m), 3.31 (2H, q), 3.95 (1H, m), 4.28 (1H, s), 5.30 (1H, bs), 6.06 (1H, d), 6.96 (1H, t), 7.15-7.44 (12H, m), 8.34 (1H, d), 10.20 (1H, s).

EXAMPLE 60

2-[N'-(2-n-Butylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

To a solution of 2-[N'-(2-aminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (500mg, 1.0mmol), obtained as described in Example 26, and n-butyraldehyde (88µl, 1.1 mmol), was added acetic acid (59µl) and a few minutes later sodiumborohydride triacetate (305mg, 1.4mmol) at room temperature. After 12 hours, the excess sodiumborohydride triacetate was destroyed by 10% $NaHCO_3$ solution (10ml) and the mixture was extracted with ethyl acetate. The organic layer dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (AcOEt 90/ MeOH 10/ $NH_4OH$ 1) to give 2-[N'-(2-n-butylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide(110mg, 20%): mp 148-150 °C; $^1$H NMR ($CDCl_3$) 0.91 (3H, t), 1.28-1.61 (9H, m),1.7 (2H, t), 2.35 (1H,bs), 2.61 (2H, t), 2.78 (2H, t), 2.88-2.92 (2H, m), 3.27-3.38 (4H, m), 4.24 (1H, s), 5.37 (1H, bt), 6.39 (1H, bt), 6.92 (1H, t), 7.13-7.40 (12H, m), 8.35 (1H, d), 10.19 (1H, s).

The following compound (Example 61) was prepared in a similar manner, but replacing n-butyraldehyde with acetone.

EXAMPLE 61

2-[N'-(2-Isopropylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

Yield 59.0%; ; $^1$H NMR ($CDCl_3$) 1.06 (6H, d), 1.35-1.88 (8H, m), 2.75-2.93 (2H,1H,2H, m,h,t), 2.93-3.37 (4H, m), 4.24 (1H, s), 5.20(1H, bt), 6.31 (1H, bt), 6.94 (1H, t), 7.14-7.43 (12H, m), 8.37 (1H, d), 10.23 (1H, s).

The following Examples (Example 62 and 63) illustrate pharmaceutical compositions according to the present invention and an "active ingredient" in these Examples is any compound of the formula(1) as hereinabove defined, preferably one of the compounds of Examples 1 to 61.

EXAMPLE 62

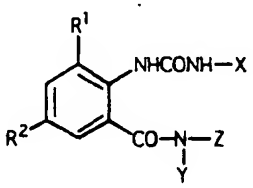
Tablet formulation: Tablets each containing 100mg of active ingredient, 200mg of lactose, 40mg of cellulose and 5mg of magnesium stearate were prepared in accordance with usual procedure.

EXAMPLE 63

Capsule formulation: Hard-shell gelatin capsules each containing 50mg of active ingredient, 100mg of lactose, 30mg of cornstarch and 2mg of magnesium stearate were prepared in accordance with usual procedure.

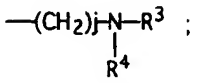
## Claims

1. A compound of 2-ureido-benzamide derivative of the formula(1)



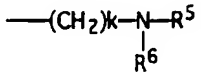

(1)

in which $R^1$ is H, halogen atom, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy or ($C_1$-$C_4$)dialkylamino and $R^2$ is H, halogen atom, hydroxy, nitro, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy or



wherein j is an integer of from 0 to 2 and $R^3$ and $R^4$ are each independently H,($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkanoyl, ($C_1$-$C_4$)alkylsulfonyl or ($C_1$-$C_4$)alkylcarbamoyl, or $R^3$ and $R^4$ can be taken together to form pyrrolidine, piperidine, morpholine, imidazole or pyrazole ring;

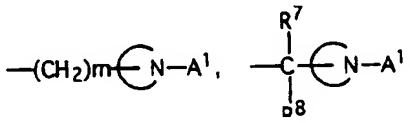
X is a group of ($C_3$-$C_{15}$)alkyl or



;

wherein k is an integer of from 1 to 4 and $R^5$ and $R^6$ are each independently H, ($C_1$-$C_6$) alkyl or ($C_1$-$C_4$)alkoxycarbonyl; and

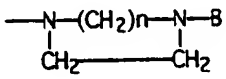
Y is H or ($C_1$-$C_4$)alkyl and Z is



or —($CH_2$)m-$A^2$ ;
wherein m is an integer of from 0 to 4,

is pyrrolidinyl or piperidyl ring and $A^1$ is phenyl, benzyl, diphenylmethyl, pyridyl, imidazolyl, imidazolylthio, dibenzoxepinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, ($C_1$-$C_7$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkoxymethyl, phenyl or halogenophenyl, and $A^2$ is phenyl, benzyl, diphenylmethyl, imidazolylthio, dibenzoxecpinyl or phenoxycarbonyl optionally carrying halogen atom, hydroxy, ($C_1$-$C_7$)alkyl, ($C_1$-$C_4$) alkoxy, ($C_1$-$C_4$)alkoxymethyl, phenyl or halogenophenyl, and $R^7$ is H or ($C_1$-$C_4$)alkyl and $R^8$ is ($C_1$-$C_4$)alkyl or $R^7$ and $R^8$ can be taken together to form cyclopentyl, cyclohexyl or cycloheptyl ring; or

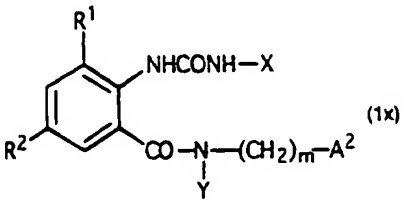
Y and Z can be taken together to form



wherein n is an integer of from 1 to 3 and B is phenyl, diphenylmethyl or dibenzocycloheptenyl optionally carrying halogen atom or ($C_1$-$C_4$)alkoxy;

or its pharmaceutically acceptable acid addition salts.

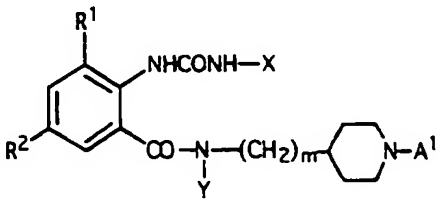
2. A compound of claim 1 in which 2-ureido-benzamide derivative of the formula(1) is a compound of the formula(1x)



(1x)

wherein $R^1$ is H; X is $(C_4\text{-}C_{10})$alkyl; and Y is H.

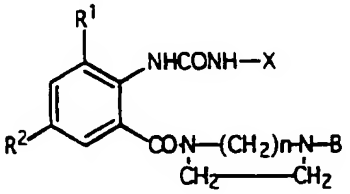
3. A compound of claim 1 in which 2-ureido-benzamide derivative of the formula(1) is a compound of the formula(1y)



(1y)

wherein $R^1$ is H; X is $(C_4\text{-}C_{10})$alkyl; and Y is H.

4. A compound of claim 1 in which 2-ureido-benzamide derivative of the formula(1) is a compound of the formula(1z)



(1z)

wherein $R^1$ is H and X is $(C_4\text{-}C_{10})$alkyl.

5. A compound of claim 2 of the formula(1x) wherein $R^2$ is H; X is $(C_4\text{-}C_8)$alkyl; m is 1 or 2; and $A^2$ is diphenylmethyl or dibenzoxepinyl.

6. A compound of claim 3 of the formula(1y) wherein $R^2$ is H or di$(C_1\text{-}C_4)$alkylamino; X is $(C_4\text{-}C_8)$alkyl; m is 0, 1 or 2; and $A^1$ is diphenylmetyl optionally carrying halogen atom or $(C_1\text{-}C_4)$alkoxy on the phenyl ring or phenoxycarbonyl.

7. A compound of claim 4 of the formula(1z) wherein $R^2$ is H; n is 2 or 3; and B is diphenylmethyl or dibenzocycloheptenyl.

8. A compound of any one of claims 1 to 7 in which 2-ureido-benzamide derivative of the formula(1) is

- 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;

- 2-(N'-n-decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-heptylureido)-N-(1-phenoxycarbonylpiperidin-4-yl)benzamide;
- 2-(N'-n-heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide;
- 2-(N'-n-heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-heptylureido)-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylhomopiperazine;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,b]cyclohepten-5-yl)piperazine;
- 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- N-(2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)benzamide;
- 2-(N'-n-heptylureido)-5-acetoamido-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- N-(3,3-diphenylpropyl)-2(N'-n-heptylureido)benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylpiperazine.

9. A pharmaceutical composition for inhibiting acyl-CoA:cholesterol acyltransferase which comprises a 2-ureido-benzamide derivative of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

10. A pharmaceutical composition for inhibiting macrophagic acyl-CoA:cholesterol acyltransferase which comprises a 2-ureido-benzamide derivative of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

11. A pharmaceutical composition for inhibiting accumulation of cholesterol ester in arterial wall which comprises a 2-ureido-benzamide derivative of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

12. Use of a 2-ureido-benzamide derivative of any one of claims 1 to 11 for the production of a medecine for use in the prevention and treatment of disorders or diseases associated with acyl-CoA:cholesterol acyltransferase, such as atherosclerosis.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number
EP 95 40 1049

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
|---|---|---|---|
| Y | JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 11, 1993 pages 1641-1653, T. KIMURA ET AL. * page 1641, abstract and left-hand column, first paragraph; page 1646, compound 38; Table III * --- | 1,2,9-12 | C07D211/26 C07D211/56 C07D211/58 C07D213/75 C07D207/09 C07D233/54 C07D233/84 C07D295/18 C07D313/12 C07D401/06 C07D401/12 C07D405/04 C07C275/28 C07C275/34 A61K31/17 A61K31/445 |
| D,Y | EP-A-0 477 778 (EISAI CO., LTD.) * claims 1,18-23; example 158 * --- | 1,2,9-12 | |
| A,D | US-A-4 623 662 (V.G. DE VRIES) * column 9, line 17 - line 39; claim 1 * --- | 1,9-12 | |
| A D | EP-A-0 335 374 (WARNER-LAMBERT CO.) * claims 1,3,4 * & US-A-5 116 848 --- | 1,9-12 | |
| A,D | EP-A-0 335 375 (WARNER-LAMBERT CO.) * claims 1,4,5 * --- | 1,9-12 | |
| A | PATENT ABSTRACTS OF JAPAN vol. 9 no. 36 (C-266) ,15 February 1985 & JP-A-59 181257 (CHUGAI SEIYAKU K.K.) 15 October 1984, * formula I * * abstract; example * --- | 1 | TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D C07C A61K |
| A | EP-A-0 235 878 (BEECHAM GROUP PLC) * page 27, compound 34 * --- | 1 | |
| A | INDIAN JOURNAL OF CHEMISTRY, vol. 26b, no. 12, 1987 pages 1133-1139, B.P. ACHARYA ET AL. * page 1134, compound 16 * --- -/-- | 1 | |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| BERLIN | 11 October 1995 | Hass, C |

CATEGORY OF CITED DOCUMENTS

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L : document cited for other reasons

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# EUROPEAN SEARCH REPORT

Application Number
EP 95 40 1049

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
|---|---|---|---|
| A | MONATSHEFTE FUR CHEMIE, vol. 98, no. 3, 1967 pages 633-642, W. METLESICS ET AL. * page 638, compound 15 * --- | 1 | |
| A | US-A-3 812 168 (K. HOEGERLE ET AL.) * column 1, abstract * ----- | 1 | |
| | | | TECHNICAL FIELDS SEARCHED (Int.Cl.6) |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| BERLIN | 11 October 1995 | Hass, C |

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